UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,269	06/01/2006	Stefan Arnold	LNK-009	3141

31496 7590 01/22/2008

SMITH PATENT CONSULTING CONSULTING, LLC
3309 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
01/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,269	ARNOLD ET AL.	
	Examiner	Art Unit	
	REGINA M. DEBERRY	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 14 November 2007 has been entered in full. New claim 14 was added. Claims 1-14 are under examination.

Withdrawn Objections And/Or Rejections

The rejection to claims 7 and 8 under 35 U.S.C. 102(e) as being anticipated by Canning et al., U.S. Patent No. 6,979,442 B1, as set forth at pages 2-3 of the previous Office Action (22 August 2007), is *withdrawn* in view of Applicant's arguments regarding MPEP 2131.03 and the claim's recitation of narrower ranges of pH 5.9-6.8 and 6.2-6.6 (14 November 2007).

The rejection to claims 2-4 and 6 under 35 U.S.C. 103(a) as being unpatentable over Canning et al. as applied to claim 1, and further in view of Sharma et al., U.S. Patent Application US 2003/0148938 A1 and Naeff et al., U.S. Patent No. 6,645,522 B2 as set forth at pages 3-5 of the previous Office Action (22 August 2007), is *withdrawn* in view of Applicant's arguments regarding MPEP 2131.03, the claim's recitation of narrower ranges of 10-200 mM and 20-100 mM of tris(hydroxymethyl)methylglycine (TRIS) and Canning et al. disclosure of ranges from 50 mM-2000 mM of TRIS (14 November 2007).

The rejection to claims 9-11 and 13 under 35 U.S.C. 103(a) as being unpatentable over Canning et al. as applied to claim 1, and further in view of Woog et al., U.S. Patent No. 4,992,419, as set forth at pages 5-6 of the previous Office Action

(22 August 2007), is *withdrawn* in view of Applicant's arguments that Woog et al. teach away from independent claim 1 by disclosing a composition comprising EPO and amino acids (14 November 2007).

Claim Rejections-35 USC § 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 5 remain rejected under 35 U.S.C. 102(e) as being anticipated by Canning et al., U.S. Patent No. 6,979,442 B1. The basis for this rejection is set forth at pages 2-3 of the previous Office Action (22 August 2007).

Applicant states that on the issue of anticipation, it is well settled that a genus disclosure will not always anticipate a claim to a particular species within the genus. Applicant cites MPEP 2131.02, *Ex parte A, 17 USPQ2d (BPAI, 1990)* and *In re*

Petering, 301 F.2d 676, 133 USPG 275 (CCPA 1962). Applicant argues that Canning is particularly directed to stabilized G-CSF compositions, though other exemplary proteins are included. Applicant states that Canning discloses HEPES, TES and TRICINE as particularly preferred and exemplified other stabilizing buffers including tris(hydroxymethyl)methylglycine. Applicant argues that it is readily apparent that the wide range of alternatives disclosed by Canning gives rise to a virtually unlimited number of possible combinations and that the pending claims are directed to only one select species within this genus, namely an unexpectedly stable pharmaceutical formulation of erythropoietin (EPO) stabilized with tris-(hydroxymethyl)-aminomethane (TRIS), a formulation that excludes the amino acid and human serum albumin stabilizer that are conventional in the prior art EPO formulations. Applicant argues that the likelihood of arriving at a composition comprised of these two select components (EPO and TRIS) "would be the same as discovering the combination of a safe by the inspection of its dials". Applicant cites Ex parte Garvey, 41 USPQ 583 (POBA 1939) and Ex parte Starr, 44 USPQ 545 (POBAA 1938). Applicant argues that the generic teachings of Canning cannot anticipate the species presently claim.

Applicant's arguments have been fully considered but are not deemed persuasive. MPEP 2131.02 states a genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species is anticipated no matter how many others are additionally named. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

Canning et al. teach stabilized protein (i.e. genus) pharmaceutical compositions comprising stabilizing buffers (i.e. genus) (abstract). Canning et al. teach a composition comprising granulocyte-colony stimulating factor (G-CSF). Canning et al. clearly teach other proteins suitable for the stabilized protein composition of the invention to include erythropoietin (EPO) (column 9, lines 32-41 and column 10, line 27). Canning et al. teach "stabilizing buffer" to mean any of several buffers that when combined with the protein of the stabilized composition, provide for a stabilized protein composition (column 13, lines 38-60). Canning et al. teach stabilizing buffers including HEPES, TES and TRICINE. Canning et al. clearly teach other stabilizing buffers to include tris-(hydroxymethyl)-aminomethane (TRIS)(column 13, line 56-57). Canning et al. teach that the stabilizing buffer is present in a concentration ranging from about 0.005M to about 2M (column 4, lines 28-31). Furthermore, no particular degree of stabilization is required and Canning teaches that all of the components being added are known to stabilize proteins. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 12 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Canning et al. as applied to claim 1 above, and further in view of Konings et al., U.S. Patent No. 5,376,632. The teachings of Canning et al. are described above. Canning et al. do not teach a pharmaceutical formulation comprising EPO and TRIS **with** ethylenediaminetetraacetic (EDTA) acid in an amount of 0.1 to 0.5 mM. The basis for this rejection is set forth at pages 6-7 of the previous Office Action (22 August 2007).

Applicant argues that the Examiner has failed to set forth a prima facie case of obviousness. Applicant argues that Konings et al. fail to provide motivation to combine EPO with TRIS stabilizer in the absence of amino acids and human serum albumin. Applicant argues that the reference teaches away from such a combination by disclosing an EPO formulation that expressly requires modified beta or gamma cyclodextrin for stabilization.

Applicant's arguments have been fully considered but are not deemed persuasive. MPEP 2141.02 [R-5] VI states that the prior art's mere disclosure of more

than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed. *In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146* (Fed. Cir. 2004). The Konings reference does not discredit or otherwise discourage pharmaceuticals comprising EPO with TRIS. The Konings reference does not teach a required use of amino acids or human serum albumin. Thus it is unclear how the Konings reference teaches away from the instant claims. Furthermore, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. Please see the recent Board decision Ex parte Smith, USPQ2d, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007)(citing KSR, 82 USPQ2d at 1396). Konings et al. teach that trace amounts of heavy metal ions can catalyze the degradation of EPO, thus it may further be appropriate to add a suitable complexing agent such as EDTA. Therefore, it would have been obvious to one having ordinary skill in the art to combine EPO and TRIS with EDTA because Konings et al. teach the use of EDTA to achieve the results of reducing the degradation of EPO. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Canning et al., U.S. Patent No. 6,979,442 B1 in view of Williams et al., US Patent Application Publication US 2004/0022861 and Sharma et al., U.S. Patent Application US 2003/0148938 A1 (reference of record).

The teachings of Canning et al. are described above in the maintained 102(e) rejection. Canning et al. do not teach a pharmaceutical formulation comprising EPO and **10-200 mM** TRIS **with 5-50 mM sodium phosphate buffer and 50-100 mM NaCl.**

Williams et al. teach drug particle formulations (abstract and paras 0003-0005). Williams et al. teach the production of pharmaceutical drug formulations by spray freezing the formulation into liquid (para 0021). Examples of proteins that can be used in the invention include EPO (para 0094). Williams et al. teach the use of 50 mM TRIS with insulin particles (para 0161)(**applies to claims 2 and 8**). The formulation can be dispersed in an aqueous vehicle which includes Tween 80 and sodium chloride (NaCl), (para 0119). A pH adjusting agent can be added for example, carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide or the like (para 0122).

Sharma et al. teach aqueous pharmaceutical formulations comprising EPO and a carboxymethyl ether cellulose polymer (para 0011-0023 and claims). Sharma et al. teach the use of sodium phosphate dibasic/monobasic as a buffering agent (**applies to claim 6**). Sharma et al. teach that the amount of buffering agent useful in the pharmaceutical compositions of the present invention depends largely on the particular buffer used and the desired pH of the formulation. Sharma et al. teach that suitable

buffering systems to maintain the pH range of about 4-9 include, but are not limited to sodium phosphate dibasic/monobasic. A pH adjusting agent such as hydrochloric acid, citric acid, sodium hydroxide, sodium citrate or a salt of any of these may be added to the formulation to adjust the pH range. Sharma et al. teach EPO pharmaceutical formulations at a pH range of 6.5-7.4 (claims 1-6)(**applies to claims 7 and 14**). Sharma et al. teach that the concentration of buffering ions will generally range from about 10 mM to about 30 mM (para 0037). Sharma et al. teach the use of NaCl as an ionic tonicity agent in the pharmaceutical composition. The use of NaCl as a tonicity agent is employed at a concentration of about 75 mM to about 100 mM. Shaef et al. also teach the use of NaCl to render formulations iso-osmotic with human blood (para 0039)(**applies to claims 3 and 4**).

Applicant argues the three basic criteria of prima facie case of obviousness; motivation, expectation of success, and that the references when combined must teach or suggest all of the claim limitations. Applicant argues that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based on Applicant's disclosure. Applicant states, "on the issue of motivation, it is important to note that the burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done." Applicant states, "to support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed to have been obvious in light of the teachings of

the references." Applicant states, "merely suggesting that a reference could be physically modified does not render the resulting modification obviousness unless the prior art also suggest the desirability of the modification". Applicant argues that while Sharma may arguably suggest the exchange of Canning's TRIS stabilizing buffer for the sodium phosphate buffer systems disclosed, there is no suggestion to modify the Canning composition to formulate a composition with both TRIS *and* sodium phosphate together.

Applicant's arguments have been fully considered but are not deemed persuasive. As was stated above, KSR forecloses the argument that *a specific teaching, suggestion or motivation* is required to support a finding of obviousness. KSR provides exemplary rationales that may support a conclusion of obviousness. One of the rationales includes "Combining Prior Art Elements According to Known Methods To Yield Predictable Results". The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. TRIS is known as a stabilizing buffer. Sodium phosphate dibasic/monobasic is known as a buffering agent. NaCl is known to render pharmaceutical formulations iso-osmotic. In combination, each element (in the instant case TRIS, sodium phosphate and NaCl) would have performed the same function as it did separately. Thus, it would have been obvious to one having ordinary skill in the art to combine EPO and TRIS with sodium phosphate buffer and

NaCl. One skilled in the art would want a stable, properly buffered, iso-osmotic pharmaceutical formulation.

Claims 1, 9-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Canning et al., U.S. Patent No. 6,979,442 B1 in view of Cho et al., U.S. Patent No. 5,656,289.

The teachings of Canning et al. are described above in the maintained 102(e) rejection. Canning et al. do not teach a pharmaceutical formulation comprising EPO and TRIS **with 0.005-0.1 %w/v** of polysorbate.

Cho et al. teach pharmaceutical formulations comprising EPO and polysorbate 20 or polysorbate 80. Cho et al. teach ranges of **0.005-0.1 %w/v** polysorbate 20 or polysorbate 80 (abstract; column 3, lines 22-39; column 7, line 59-column 8, line 15; column 10, lines 25-38 and column 20, lines 40-45). Polysorbate 20 and polysorbate 80, commercially branded as Tween 20 and Tween 80, respectively, are well-known in the art as polysorbates surfactants used as detergents and/or emulsifiers in pharmaceutical compositions. Thus, it would have been obvious to one having ordinary skill in the art to combine EPO and TRIS with polysorbate (Tween 20 or Tween 80) to yield the predictable results of acting as a detergent and/or emulsifier in pharmaceutical compositions.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to REGINA M. DEBERRY whose telephone number is (571)272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD 1/16/08